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**Smyd3 regulates cancer cell phenotypes and catalyzes histone H4 lysine 5 methylation.**

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**Public Summary:**

This study determines the target of the Smyd3 enzyme on the chromatin of cells. The chromatin is the mixture of DNA and proteins in the nucleus of cells. Smyd3 adds methyl groups to the chromatin, which influences gene expression.

**Scientific Abstract:**

Smyd3 is a lysine methyltransferase implicated in chromatin and cancer regulation. Here we show that Smyd3 catalyzes histone H4 methylation at lysine 5 (H4K5me). This novel histone methylation mark is detected in diverse cell types and its formation is attenuated by depletion of Smyd3 protein. Further, Smyd3-driven cancer cell phenotypes require its enzymatic activity. Thus, Smyd3, via H4K5 methylation, provides a potential new link between chromatin dynamics and neoplastic disease.

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